

In re Application of  
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Attorney Docket No.: MBM1240

## REMARKS

Claims 1, 3-8, 15, 16, 20-22, 48-57 are pending and are subject to restriction/election. Claims 48, 49, 51, 52 stand withdrawn from consideration as a non-elected invention under a restriction requirement. New claims 58-61 have been added. These claims add no new matter and are supported throughout the specification; for example, support for claim 58 may be found in original claim 1, or in paragraph [0053]; support for claims 59 and 60 may be found in paragraphs [0091], [0097], or in Examples II, III, or IV; and support for claim 61 may be found in Example IV.

### Restriction Requirement

While reiterating the grounds for election with traverse of invention I with an election of species of MS, as set out in Paper No. 11, filed 3/27/0, Applicant notes the withdrawal of claims 48, 49, 50, and 51, and the finality of the restriction requirement.

### Formal Matters

Figures 1, 3, 4, 9 and 11 were objected to on the basis that they do not allow visualization of the details discussed in the brief description of the drawings, due to the poor photocopy quality. In addition, the disclosure was objected to because the brief description of the drawings does not refer to each separately numbered figure.

Figures 1, 3, 4, 9 and 11 have been deleted, and Figures 2, 5-8, 10, and 12 have been renumbered as Figures 1-7. The brief description of the drawings has been amended to refer to each separately numbered figure, and to delete the description of Figures 1, 3, 4, 9 and 11. The detailed description of the invention has been amended to delete references to Figures 1, 3, 4, 9 and 11; to replace references to Figures 2, 5-8, 10, and 12 with the renumbered Figures 1-7; and to include the description of Figures 1, 3, 4, 9 and 11. No new matter has been added by these amendments.

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Applicant notes the objection that claims 20-22, 50 and 53-57 are a substantial duplication of claims 1, 3-8, 15 and 16 under 37 CFR 1.75, and will consider this objection upon notification of allowable subject matter.

### **Rejections Under 35 U.S.C. § 112**

Claims 1, 3, 6-8, 15, 16, 20-22, 50 and 55-57 are rejected under 35 U.S.C 112, first paragraph, as lacking enablement for the term “derivative thereof.” This term has been canceled, without prejudice:

### **Rejections Under 35 U.S.C. § 102**

Claims 1, 3-8, 15, 16, 20-22, 50, and 53-57 are rejected under 35 U.S.C. §102(b) as being anticipated by Bellgrau *et al.*, WO 95/32627 (hereafter “Bellgrau”). The Office Action asserts that Bellgrau teaches methods of using FAS ligand to suppress lymphocyte mediated immune responses, including inflammation and discloses both use of soluble FAS ligand and treatment of multiple sclerosis (MS). Claims 1, 3-8, 15, 16, 20-22, 50, and 53-57 are also rejected under 35 U.S.C. 102(b) as being anticipated by Queen *et al.*, U.S. Patent Number 6,046,310 (hereafter “Queen”). The Office Action asserts that Queen teaches methods of using FAS ligand fusion proteins to treat autoimmune diseases, including MS. The Office Action further asserts, with respect to both Bellgrau and Queen, that as MS is a disease of the central nervous system (CNS), a person of ordinary skill in the art reading the disclosure of Bellgrau would immediately grasp that the administration for treatment of MS would be to the CNS, meeting the limitation of “behind the blood-tissue barrier of the immune privileged site” in the pending claims.

The claims, as amended, provide methods of inhibiting inflammation by delivering an effective amount of a soluble Fas ligand, capable of inducing apoptosis in Fas-expressing cells, behind the blood tissue barrier of an immune privileged site. The ability of soluble Fas ligand to inhibit inflammation is surprising, in part, because full length Fas ligand was reported to have

proinflammatory effects (Ottonello et al., 1999, "Exhibit A"; Rescigno et al. 2000, "Exhibit B"; both enclosed herewith) and to induce T cell proliferation (Alderson et al. 1993, Abstract only; "Exhibit C"; enclosed herewith). Support for these amendments may be found throughout the specification at, for example, paragraph [0052] which teaches inhibition of inflammation, or at paragraph [0053], which teaches Fas ligand fragments, including soluble Fas ligand fragments.

Bellgrau suggests that cellular expression of the Fas ligand is responsible for the protection of allogeneic testicular grafts against rejection, by showing that testicular tissue or cells lacking the expression of endogenous full-length Fas ligand were rejected, whereas similar wild type tissue or cells survived, after transplantation into the kidney capsules of mice. Bellgrau asserts, based on these experiments, that Fas ligand may be used for treating inflammation. Bellgrau discloses both full length and soluble Fas ligand, but does not point to any functional differences between the two; rather Bellgrau teaches that soluble Fas ligand possesses the immunosuppressive activity of the native protein (page 11, lines 29-33). Bellgrau accordingly does not explicitly teach the delivery of a soluble Fas ligand fragment behind the blood-tissue barrier, nor does it provide any teaching from which one of skill in the art could have reasonably concluded, without unreasonable experimentation, that effective inhibition of inflammation would be achieved by the use of a soluble Fas ligand fragment delivered behind the blood-tissue barrier.

The established test for anticipation was set out in a recent U.S. Court of Appeals for the Federal Circuit decision, which held that "anticipation requires that the assertedly anticipating disclosure enabled the subject matter of the reference and thus of the patented invention without undue experimentation" (*Elan Pharmaceuticals Inc. v Mayo Foundation for Medical Education and Research*, No. 00-1467, decided October 2, 2003). It is also well established that anticipation cannot be shown by combining more than one reference, and reliance on the single source does not preclude the use of extrinsic evidence to show what a reference's disclosure signified to one of ordinary skill in the art (*Sunrise Medical HHG, Inc. v. Air Sep Corp.*, 247

F.3d 1316, 1328, 58 USPQ 2d 1545, Fed. Cir. 2001).

In the present case, the extrinsic evidence of Exhibits A through G establishes that Bellgrau's disclosure could not have been understood by one of skill in the art to teach or suggest that the use of a soluble Fas ligand fragment delivered behind the blood-tissue barrier would be effective to inhibit inflammation within an immune privileged site. A person of ordinary skill in the art, upon reading Bellgrau, would not even necessarily conclude that the absence of Fas ligand would account for the difference in graft rejection, given the fundamental differences in development that may exist between wild type and transgenic animals, and given the lack of showing of any direct link between Fas ligand and transplantation rejection or inflammation. In the present case, the extrinsic evidence includes reports showing that Bellgrau's results could not be reproduced by other researchers (Vaux 1998; "Exhibit D," enclosed herewith). The extrinsic evidence also includes studies using grafts from Fas ligand-overexpressing transgenic mice, which showed accelerated rejection, rather than protection (Allison et al. 1997, "Exhibit E"; Kang et al. 1997, Abstract only, "Exhibit F"; Takeuchi et al., 1999, "Exhibit G"; all enclosed herewith). The teaching that Fas ligand expression is associated with accelerated rejection is in agreement with the teaching exemplified in Exhibits A through C to the effect that the Fas ligand has been reported to have pro-inflammatory effects and to induce T cell proliferation.

Thus, not only does Bellgrau not demonstrate a link between soluble Fas ligand and inhibition of inflammation, but the reports of pro-inflammatory and T cell proliferative functions of Fas ligand in the prior art teach away from the present invention. Bellgrau's disclosure, in the context of the extrinsic evidence of other publications available to one of skill in the art, therefore does not enable inhibition of inflammation within an immune privileged site using a soluble Fas ligand fragment delivered behind the blood-tissue barrier. Bellgrau cannot therefore be considered an anticipating disclosure.

Turning to the Queen reference, Queen teaches fusion proteins having a functional moiety of the extracellular domain of the Fas ligand and a polypeptide capable of specifically binding to

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a cell surface marker. Queen does not teach or disclose delivering a soluble Fas ligand behind the blood tissue barrier of an immune privileged site, as is claimed in the present application, and therefore does not teach every element of the present claims, as is required for a reference to be considered an anticipating disclosure (M.P.E.P § 2131), or enable treatment or modulation of inflammation.

With respect to the Examiner's assertion that a person of ordinary skill in the art, upon reading Bellgrau or Queen, would immediately grasp that administration for treatment of MS would be to the CNS, Applicant respectfully submits that many current MS therapies are administered systemically. Multiple alternative treatments for MS have been approved by the FDA, including Interferon Beta-1a and Interferon Beta-1b, Glatiramer acetate, and mitoxantrone (see "Exhibit H," submitted herewith). All of these treatments are normally administered systemically by intramuscular, subcutaneous, or intravenous injection (Exhibit H, column 4), and therefore do not meet the limitation of delivery "behind the blood-tissue barrier of the immune privileged site." Therefore, Applicant submits that a person of ordinary skill in the art would not immediately grasp that the administration for treatment of MS would be to the CNS upon reading Bellgrau or Queen.

Applicant therefore respectfully submits that the claims are not anticipated by Bellgrau or Queen.

### **Conclusion**

Applicant submits that the claims as amended are novel, non-obvious, and supported by the description, and respectfully requests that a timely Notice of Allowance be issued in this case.

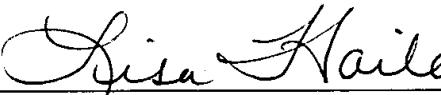
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A check in the amount of \$210.00 is enclosed for the two month Extension of Time fee. The Commissioner is hereby authorized to charge any other fees that may be associated with this communication, or credit any overpayment to Deposit Account No. 50-1355.

Respectfully submitted,

Date: November 18, 2003

  
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